

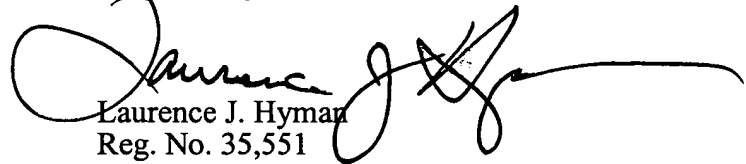
Keith E. Mostov, et al.  
Application No.: 09/818,247  
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PATENT

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Respectfully submitted,



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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**IN THE SPECIFICATION:**

Please replace the paragraph beginning on page 3, line 9, with the following rewritten paragraph:

In some preferred embodiments, the ligands bind to a peptide derived from human pIgR (SEQ ID NO: [2] 1), which peptide is selected from the group consisting of: Lys487-Arg603, Lys487-Glu607, Lys487-Val611, Lys487-Arg615, Lys487-Ala618, Cys520-Arg603, Cys520-Glu607, Cys520-Val611, Cys520-Arg615, Cys520-Ala618, Lys577-Arg603, Lys577-Glu607, Lys577-Val611, Lys577-Arg615, Lys577-Ala618, Ser574-Arg603, Ser574-Glu607, Ser574-Val611, Ser574-Arg615, Ser574-Ala618, Val560-Arg603, Val560-Glu607, Val560-Val611, Val560-Arg615, Val560-Ala618, Cys544-Arg603, Cys544-Glu607, Cys544-Val611, Cys544-Arg615, and Cys544-Ala618. In some particularly preferred embodiments, the ligands bind to an epitope selected from the group consisting of QDPRLF (SEQ ID NO:10), LDPRLF (SEQ ID NO:11), KAIQDPRLF (SEQ ID NO:12), LDPRLFADEREI (SEQ ID NO:13), DENKANLDPRLF (SEQ ID NO:14), RLFADEREI (SEQ ID NO:15), and LDPRLFAD (SEQ ID NO:16). The organ of interest may be selected from the group consisting of a small intestine, a large intestine, a liver-biliary tree, a salivary gland, a stomach, a lung, a vagina, a uterus, a lacrimal gland, a mammary gland, a nasal passage, and a sinus.

Please replace the paragraph beginning on page 4, line 6, with the following rewritten paragraph:

In another group of embodiments, the invention provides a method of introducing a ligand into a cell of an organ of interest in an animal, which cell expresses a polymeric immunoglobulin receptor, by binding the ligand to a region of the polymeric

immunoglobulin receptor, with the provisos that (a) the ligand does not substantially bind to a form of secretory component which is the most abundant form present in the organ of interest under physiological conditions and (b) the ligand does not substantially bind to a stalk region of the pIgR, thereby permitting introduction of the ligand into the cell. In some of these embodiments, the ligand is an antibody, and may be a recombinant single chain variable region fragment of an antibody, or a disulfide stabilized variable region fragment, either of which may be humanized. The ligand can selectively bind to a peptide derived from human pIgR (SEQ ID NO:[2]1), which peptide is selected from the group consisting of: Lys487-Arg603, Lys487-Glu607, Lys487-Val611, Lys487-Arg615, Lys487-Ala618, Cys520-Arg603, Cys520-Glu607, Cys520-Val611, Cys520-Arg615, Cys520-Ala618, Lys577-Arg603, Lys577-Glu607, Lys577-Val611, Lys577-Arg615, Lys577-Ala618, Ser574-Arg603, Ser574-Glu607, Ser574-Val611, Ser574-Arg615, Ser574-Ala618, Val560-Arg603, Val560-Glu607, Val560-Val611, Val560-Arg615, Val560-Ala618, Cys544-Arg603, Cys544-Glu607, Cys544-Val611, Cys544-Arg615, and Cys544-Ala618. In some preferred embodiments, the ligand binds to an epitope selected from the group consisting of QDPRLF (SEQ ID NO:10), LDPRLF (SEQ ID NO:11), KAIQDPRLF (SEQ ID NO:12), LDPRLFADEREI (SEQ ID NO:13), DENKANLDPRLF (SEQ ID NO:14), RLFADEREI (SEQ ID NO:15), and LDPRLFAD (SEQ ID NO:16).

Please replace the paragraph beginning on page 5, line 24, with the following rewritten paragraph:

The invention further provides ligands that binds specifically to a region of a polymeric immunoglobulin receptor (pIgR) of a cell, provided that binding of the ligand reduces proteolytic cleavage of secretory component (SC) by at least one-third compared to the cleavage of SC from a cell in the absence of binding of the ligand and provided further that the ligand does not substantially bind to a stalk of said pIgR remaining after proteolytic cleavage under physiological conditions. The ligand may be an antibody, a scFv, a recombinant single chain variable region fragment of an antibody,

a disulfide stabilized variable region fragment ("dsFv"), a humanized scFv, or a humanized dsFv. The ligands may bind to a peptide derived from human pIgR (SEQ ID NO:[2]1), selected from the group consisting of: Lys487-Arg603, Lys487-Glu607, Lys487-Val611, Lys487-Arg615, Lys487-Ala618, Cys520-Arg603, Cys520-Glu607, Cys520-Val611, Cys520-Arg615, Cys520-Ala618, Lys577-Arg603, Lys577-Glu607, Lys577-Val611, Lys577-Arg615, Lys577-Ala618, Ser574-Arg603, Ser574-Glu607, Ser574-Val611, Ser574-Arg615, Ser574-Ala618, Val560-Arg603, Val560-Glu607, Val560-Val611, Val560-Arg615, Val560-Ala618, Cys544-Arg603, Cys544-Glu607, Cys544-Val611, Cys544-Arg615, and Cys544-Ala618. In one set of embodiments, the ligand binds to an epitope selected from the group consisting of QDPRLF (SEQ ID NO:10), LDPRLF (SEQ ID NO:11), KAIQDPRLF (SEQ ID NO:12), LDPRLFADEREI (SEQ ID NO:13), DENKANLDPRLF (SEQ ID NO:14), RLFADEREI (SEQ ID NO:15), and LDPRLFAD (SEQ ID NO:16).

Please replace the paragraph beginning on page 6, line 27, with the following rewritten paragraph:

In another set of embodiments, the invention provides methods of introducing a ligand into a cell expressing a polymeric immunoglobulin receptor (pIgR) by attaching the ligand to a region of the pIgR, provided that (a) binding of the ligand reduces proteolytic cleavage of secretory component (SC) by at least one-third compared to the cleavage of SC from a cell in the absence of the ligand, and (b) the ligand does not substantially bind to a stalk of said pIgR remaining after proteolytic cleavage under physiological conditions, thereby permitting introduction of the ligand into the cell. The ligand may be, for example, an antibody, a humanized antibody, a scFv, a recombinant single chain variable region fragment of an antibody, or a disulfide stabilized variable region. The ligand preferably binds to a peptide derived from human pIgR (SEQ ID NO: [2]1), selected from the group consisting of: Lys487-Arg603, Lys487-Glu607, Lys487-Val611, Lys487-Arg615, Lys487-Ala618, Cys520-Arg603, Cys520-Glu607, Cys520-Val611, Cys520-Arg615, Cys520-Ala618, Lys577-Arg603, Lys577-Glu607, Lys577-

Val611, Lys577-Arg615, Lys577-Ala618, Ser574-Arg603, Ser574-Glu607, Ser574-Val611, Ser574-Arg615, Ser574-Ala618, Val560-Arg603, Val560-Glu607, Val560-Val611, Val560-Arg615, Val560-Ala618, Cys544-Arg603, Cys544-Glu607, Cys544-Val611, Cys544-Arg615, and Cys544-Ala618. In some embodiments, the ligand binds to an epitope of pIgR selected from the group consisting of QDPRLF (SEQ ID NO:10), LDPRLF (SEQ ID NO:11), KAIQDPRLF (SEQ ID NO:12), LDPRLFADEREI (SEQ ID NO:13), DENKANLDPRLF (SEQ ID NO:14), RLFADEREI (SEQ ID NO:15), and LDPRLFAD (SEQ ID NO:16). The ligand may have a binding component for selectively binding to a region of pIgR and a biologically active component. The biologically active component may be selected from the group consisting of: a nucleic acid, a protein, a radioisotope, a lipid, a carbohydrate, a peptidomimetic, an anti-inflammatory, an antibiotic, and an anti-infective. In one set of embodiments, the biologically active component is a small molecule. The animal can be a mammal. In one embodiment, the biologically active component is a nucleic acid encodes the wildtype cystic fibrosis transmembrane conductance regulator. The cell can be a mammalian cell, especially an epithelial cell. The ligand can bind to the pIgR at the apical surface of the cell. The ligand can then be transcytosed to the basolateral side of the cell, and may remain attached or can be released from the pIgR at the basolateral surface of the cell. The SC can exist in several forms in an organ of interest, provided that the ligand (a) does not bind to the most abundant form of SC present in the organ of interest, and (b) does not bind to a stalk remaining on an extracellular surface of a cell of the organ of interest after pIgR cleavage. The organ of interest can be selected from the group consisting of a small intestine, a large intestine, a liver-biliary tree, a stomach, a salivary gland, a lung, a vagina, a uterus, a lacrimal gland, a mammary gland, a nasal passage, and a sinus.

Please replace the paragraph beginning on page 8, line 25, with the following rewritten paragraph:

The ligand may selectively bind to a peptide derived from human pIgR (SEQ ID NO: [2]1), which peptide is selected from the group consisting of: Lys487-

Arg603, Lys487-Glu607, Lys487-Val611, Lys487-Arg615, Lys487-Ala618, Cys520-Arg603, Cys520-Glu607, Cys520-Val611, Cys520-Arg615, Cys520-Ala618, Lys577-Arg603, Lys577-Glu607, Lys577-Val611, Lys577-Arg615, Lys577-Ala618, Ser574-Arg603, Ser574-Glu607, Ser574-Val611, Ser574-Arg615, Ser574-Ala618, Val560-Arg603, Val560-Glu607, Val560-Val611, Val560-Arg615, Val560-Ala618, Cys544-Arg603, Cys544-Glu607, Cys544-Val611, Cys544-Arg615, and Cys544-Ala618. In one set of preferred embodiments, the ligand may bind to an epitope selected from the group consisting of QDPRLF (SEQ ID NO:10), LDPRLF (SEQ ID NO:11), KAIQDPRLF (SEQ ID NO:12), LDPRLFADEREI (SEQ ID NO:13), DENKANLDPRLF (SEQ ID NO:14), RLFADEREI (SEQ ID NO:15), and LDPRLFAD (SEQ ID NO:16). In some embodiments of the method, the ligand may further be defined as having a binding component for selectively binding to pIgR and a biologically active component. The biologically active component is selected from the group consisting of a nucleic acid, a peptide, a protein, a radioisotope, a lipid, a carbohydrate, a peptidomimetic, an anti-inflammatory, an antisense oligonucleotide, an antibiotic, and an anti-infective. In one set of embodiments, the biologically active component can be a small molecule. The method can be used with respect to a mammalian cell, and especially where the cell is an epithelial cell. The organ of interest can be selected from the group consisting of a small intestine, a large intestine, a liver-biliary tree, a stomach, a salivary gland, a lung, a vagina, a uterus, a lacrimal gland, a mammary gland, a nasal passage, and a sinus.

Please replace the paragraph beginning on page 9, line 24, with the following rewritten paragraph:

The invention additionally provides a method of transcytosing a ligand from an apical to a basolateral side of a cell of an organ of interest in an animal, which cell expresses a polymeric immunoglobulin receptor (pIgR), by attaching the ligand to a region of the pIgR, provided that (a) binding of the ligand reduces proteolytic cleavage of secretory component (SC) by at least one-third compared to the cleavage of SC from a cell in the absence of the ligand, and (b) the ligand does not substantially bind to a stalk

of said pIgR remaining after proteolytic cleavage under physiological conditions, thereby permitting transcytosis of the ligand from the apical side to the basolateral side of the cell. The ligand can be, for example, an antibody, including a humanized antibody, a scFv (including a recombinant single chain variable region fragment of an antibody), and a disulfide stabilized variable region. The ligand can bind to a peptide derived from human pIgR (SEQ ID NO:1), selected from the group consisting of: Lys487-Arg603, Lys487-Glu607, Lys487-Val611, Lys487-Arg615, Lys487-Ala618, Cys520-Arg603, Cys520-Glu607, Cys520-Val611, Cys520-Arg615, Cys520-Ala618, Lys577-Arg603, Lys577-Glu607, Lys577-Val611, Lys577-Arg615, Lys577-Ala618, Ser574-Arg603, Ser574-Glu607, Ser574-Val611, Ser574-Arg615, Ser574-Ala618, Val560-Arg603, Val560-Glu607, Val560-Val611, Val560-Arg615, Val560-Ala618, Cys544-Arg603, Cys544-Glu607, Cys544-Val611, Cys544-Arg615, and Cys544-Ala618. In some preferred embodiments, the ligand binds to an epitope of pIgR selected from the group consisting of QDPRLF (SEQ ID NO:10), LDPRLF (SEQ ID NO:11), KAIQDPRLF (SEQ ID NO:12), LDPRLFADEREI (SEQ ID NO:13), DENKANLDPRLF (SEQ ID NO:14), RLFADEREI (SEQ ID NO:15), and LDPRLFAD (SEQ ID NO:16).

Please replace the paragraph beginning on page 11, line 20, with the following rewritten paragraph:

**Figure 2.** Figure 2 shows the sequence of human pIgR (SEQ ID NO:[17]1) as set forth in the SWISS-PROT database under accession number P01833. The amino acids in the sequence are set forth in standard single-letter code.

Please replace the paragraph beginning on page 12, line 17, with the following rewritten paragraph:

**Figure 5** Figure 5 shows the amino acid sequence (SEQ ID NO:22) of a secreted form of scFv 4A, bearing two labels: the FLAG® epitope and an epitope from the *myc* oncogene, as well as a six-histidine tail for easy purification. PelB leader: PelB leader promotes secretion of the peptide from *E. coli*. FLAG®: FLAG® epitope. Heavy

chain FR: Framework region of immunoglobulin heavy chain. Light chain FR: Framework region of immunoglobulin light chain. CDR: complementarity determining region. Numbers after the abbreviations designate the particular numbered region, e.g., CDR3 designates complementarity determining region 3, which is considered in the art to have the greatest contact with the target epitope of the antigen. Linker: linker peptide used in 4A construct (GGS=SEQ ID NO:23). myc: epitope from *myc* oncogene recognized by commercially available antibodies. 6 HIS: 6 histidine tail.

Please replace the paragraph beginning on page 30, line 14, with the following rewritten paragraph:

The nucleic acid and amino acid sequence of the polymeric immunoglobulin receptor has been identified in a variety of taxonomically diverse species. See, Piskurich *et al.*, *Journal of Immunology* 154:1735-1747 (1995). The sequence of human pIgR is set forth, *inter alia*, in Eiffert *et al.*, Hoppe Seyler's Z. Physiol. Chem. Bd. 365, S.1489-1495 (1984), and in Hughes *et al.*, FEBS Letters 410:443-446 (1997), and further set forth in SWISS-PROT, a curated protein sequence database maintained by the European Molecular Biology Laboratory Data Library, under accession number P01833 (the sequence is publicly available at, e.g., [www.expasy.ch/cgi-bin/sprot-search-ac?P01833](http://www.expasy.ch/cgi-bin/sprot-search-ac?P01833)). The numbering in SWISS-PROT (see, e.g., SEQ ID NO:[2]1) includes an 18-residue leader sequence; thus, references to particular residues in the SWISS-PROT database are 18 numbers higher than the numbers accorded the same residues by references which do not include the leader sequence (such as Hughes *et al.* and the Mostov and Kaetzel reference), even though they refer to the same protein. References herein to one or more numbered residues of human pIgR are to the residues as numbered in the SWISS-PROT database. The SWISS-PROT database also reports that an alanine to valine variant has been found at position 580 of the sequence. Ligands that bind to B regions containing this or other similar variants are encompassed within the present invention. Such variants include variants of the sequence set forth in SWISS-PROT so long as they do not destroy the function of the



variant pIgR molecule as a receptor for polymeric immunoglobulin and do not destroy the ability of the variant pIgR molecule to internalize and transcytose a ligand bound to it. Assays for determining internalization and transcytosis of a bound ligand are set forth in the Examples.

Please replace the paragraph beginning on page 33, line 1, with the following rewritten paragraph:

Mostov and Kaetzel, *supra*, reviews and summarizes much of the available information regarding SC cleavage. They note that Hughes et al., FEBS Letters 410:443-446 (1997), isolated human colostrum SC from a single individual and showed that the C terminal residue was Arg585. In contrast, earlier work published in German (Eiffert, et al, Hoppe Seyler's Z. Physiol. Chem. Bd. 365, S.1489-1495 (1984), found a "ragged" (i.e. variable C-terminus of SC from human colostrum (pooled from several individuals). The C-termini that they reported were Ala550, Gly551, Ser552, Ala558, and Lys559. (The numbering of the residues in Eiffert et al. is considered by those of skill to be off by one. The numbering of the residues set forth in the text have been corrected to their accepted numbering as set forth in the SWISS-PROT database (see SEQ ID NO: [2]1), and in other sources. For ease of reference, the numbering used by those of skill is used in the text herein. In Eiffert et al., the residues mentioned above were designated Ala449, Gly550, Ser551, Ala557, and Lys558, respectively.) The predominant species ended in Ser552.

Please replace the paragraph beginning on page 36, line 4, with the following rewritten paragraph:

In preferred embodiments, the stalk is identified by use of antibodies specific for the first 15-30 amino acids of pIgR extracellular to the transmembrane domain of the species of interest. An exemplary protocol for generating antibodies identifying the stalk region of pIgR is set forth in Example 1. Peptides that correspond to the pIgR stalks of mouse, rat, human, bovine, and rabbit are set forth as SEQ ID NOS:2,

3, 4, 5, and 6 of U.S. Patent No. 6,042,833. In particular, SEQ ID NO:4 of the '833 patent sets forth the peptide corresponding to the stalk of human pIgR as: Glu-Lys-Ala-Val-Ala-Asp-Thr-Arg-Asp-Gln-Ala-Asp-Gly-Ser-Arg-Ala-Ser-Val-Asp-Ser-Gly-Ser-Ser-Glu-Glu-Gln-Gly-Gly-Ser-Ser-Arg (SEQ ID NO:19). In preferred embodiments, the ligands of the invention do not substantially bind to an extracellular epitope within the first 33 amino acids that are cell membrane proximal to the initial pIgR cleavage site.

Please replace the paragraph beginning on page 48, line 8, with the following rewritten paragraph:

In studies with several antibodies, a version of an anti-B region antibody was developed which has proven useful in monitoring binding and transcytosis. This version of the antibody bears the "FLAG®" peptide, a label system commercially available from Sigma (St. Louis, MO). Experiments showed that scFvs labeled with the FLAG® peptide and bearing an anti-FLAG antibody could bind to B region of pIgR, undergo apical to basolateral transcytosis and be released into the basolateral medium. The amino acid sequence (SEQ ID NO:22) of an exemplary scFv labeled with the FLAG® epitope [SEQ ID NO:22], an scFv designated 4AF, is set forth in Figure 5 (the unlabeled scFv, 4A, is the same sequence, minus the FLAG® epitope). The scFv is labeled with both FLAG® and with an epitope from the *myc* oncogene. This "FLAGged" form of scFv 4A has a pelb sequence to facilitate secretion of the finished protein when produced in *E. coli* (as is well known in the art, different leader sequences would be used to facilitate secretion in other organisms), and a 6-histidine tail to facilitate purification using immobilized metal-ion affinity chromatography ("IMAC"). The unboxed "AAA" residues are part of the Not I site engineered in for cloning. Construction of the scFV is described in the Examples.

Please replace the paragraph beginning on page 50, line 19, with the following rewritten paragraph:

In some embodiments, the peptide linker is the sequence is Gly-Gly-Gly-Ser (SEQ ID NO:23), Gly-Gly-Gly-Ser-Gly-Gly-Gly (SEQ ID NO:24) (optionally, an additional Gly can be on either or both ends), or Gly-Gly-Gly-Gly-Ser (SEQ ID NO:25) or a concatamer of this sequence, and will preferably comprise 2, 3, 4, 5, or 6 copies of this sequence. It should be noted that glycine is generally preferred in peptide linkers because it is flexible, does not have a side group expected to interfere with the intended biological activity of the linked molecules, and under physiological conditions does not bear a charge. However, it is to be appreciated that some amino acid substitutions within the linker can be made. For example, a valine can be substituted for a glycine.

Please replace the paragraph beginning on page 50, line 28, with the following rewritten paragraph:

As set forth in the Examples, the epitopes to which phage displaying scFv from a human library bound were mapped using a series of 15-residue peptides. Both human pIgR and rat pIgR sequences were used for mapping. The results of the ELISAs revealed that the scFv bound primarily to regions on the N-terminal side of the major cleavage site. For example, as shown in Figure 3, scFv 4A bound to the epitope defined by the sequence QDPRLF (SEQ ID NO:10) in human pIgR (residues 600 to 605 of the human sequence as set forth in SWISS-PROT) and to the epitope defined by the sequence LDPRLF (SEQ ID NO:11) in rat pIgR [SEQ ID NO:11] (residues 605-610 of the rat pIgR sequence). Although not tested directly, it appears likely that the "Q" in the human sequence and the "L" in the rat sequence may not be necessary and that the antibody will bind to the epitope defined by the amino acids DPRLF (SEQ ID NO:26).

Please replace the paragraph beginning on page 51, line 5, with the following rewritten paragraph:

As further shown in Figure 3, the epitope LDPR[FL]LF (SEQ ID NO:11) of rat pIgR was also bound by antibody 5D, which also bound to the epitope defined by the sequence KAIQDPRLF (SEQ ID NO:12) of human pIgR. ScFv 2E bound to the

epitope defined by the sequence LDPRLFADEREI (SEQ ID NO:13) of rat pIgR. ScFv 2H bound to the epitope defined by the sequence DENKANLDPRLF (SEQ ID NO:14). ScFv 1F bound to the epitope defined by the sequence RLFADEREI (SEQ ID NO:15). ScFvs 1C, 7H, and 6B all bound to the epitope defined by the sequence LDPRLFAD (SEQ ID NO:16). Since the peptides tested were "staggered" by three residues, the more peptides the antibodies were tested against, the more it was possible to map the precise epitope to which the antibody bound.

Please replace the paragraph beginning on page 78, line 8, with the following rewritten paragraph:

The studies revealed that antibody 4A bound to the epitope defined by the sequence QDPRLF (SEQ ID NO:10) in human pIgR (residues 600 to 605 of the human sequence as set forth in SWISS-PROT) and to the epitope defined by the sequence LDPRLF (SEQ ID NO:11) in rat pIgR (residues 605-610 of the rat pIgR sequence), an epitope also bound by antibody 5D. Antibody 5D also bound to the epitope defined by the sequence KAIQDPRLF (SEQ ID NO:12) of human pIgR. ScFv 2E bound to the epitope defined by the sequence LDPRLFADEREI (SEQ ID NO:13) of rat pIgR. ScFv 2H bound to the epitope defined by the sequence DENKANLDPRLF (SEQ ID NO:14). ScFv 1F bound to the epitope defined by the sequence RLFADEREI (SEQ ID NO:15). ScFvs 5F, 10H, 1C, 7H, and 6B all bound to the epitope defined by the sequence LDPRLFAD (SEQ ID NO:16).

IN THE CLAIMS:

Please amend the claims as follows:

8. (Amended) A ligand of claim 1 which binds to a peptide derived from human pIgR (SEQ ID NO:[2]1), which peptide is selected from the group consisting of: Lys487-Arg603, Lys487-Glu607, Lys487-Val611, Lys487-Arg615, Lys487-Ala618, Cys520-Arg603, Cys520-Glu607, Cys520-Val611, Cys520-Arg615, Cys520-Ala618,

Lys577-Arg603, Lys577-Glu607, Lys577-Val611, Lys577-Arg615, Lys577-Ala618, Ser574-Arg603, Ser574-Glu607, Ser574-Val611, Ser574-Arg615, Ser574-Ala618, Val560-Arg603, Val560-Glu607, Val560-Val611, Val560-Arg615, Val560-Ala618, Cys544-Arg603, Cys544-Glu607, Cys544-Val611, Cys544-Arg615, and Cys544-Ala618.

9. (Amended) The ligand of claim 1, further wherein the ligand binds to an epitope selected from the group consisting of QDPRLF (SEQ ID NO:10), LDPRLF (SEQ ID NO:11), KAIQDPRLF (SEQ ID NO:12), LDPRLFADEREI (SEQ ID NO:13), DENKANLDPRLF (SEQ ID NO:14), RLFADEREI (SEQ ID NO:15), and LDPRLFAD (SEQ ID NO:16).

21. (Amended) A method of claim 17, wherein the ligand selectively binds to a peptide derived from human pIgR (SEQ ID NO:[2]1), which peptide is selected from the group consisting of: Lys487-Arg603, Lys487-Glu607, Lys487-Val611, Lys487-Arg615, Lys487-Ala618, Cys520-Arg603, Cys520-Glu607, Cys520-Val611, Cys520-Arg615, Cys520-Ala618, Lys577-Arg603, Lys577-Glu607, Lys577-Val611, Lys577-Arg615, Lys577-Ala618, Ser574-Arg603, Ser574-Glu607, Ser574-Val611, Ser574-Arg615, Ser574-Ala618, Val560-Arg603, Val560-Glu607, Val560-Val611, Val560-Arg615, Val560-Ala618, Cys544-Arg603, Cys544-Glu607, Cys544-Val611, Cys544-Arg615, and Cys544-Ala618.

22. (Amended) The method of claim 17, wherein the ligand binds to an epitope selected from the group consisting of QDPRLF (SEQ ID NO:10), LDPRLF (SEQ ID NO:11), KAIQDPRLF (SEQ ID NO:12), LDPRLFADEREI (SEQ ID NO:13), DENKANLDPRLF (SEQ ID NO:14), RLFADEREI (SEQ ID NO:15), and LDPRLFAD (SEQ ID NO:16).

37. (Amended) A ligand of claim 32, which binds to a peptide derived from human pIgR (SEQ ID NO:[2]1), selected from the group consisting of: Lys487-Arg603, Lys487-Glu607, Lys487-Val611, Lys487-Arg615, Lys487-Ala618, Cys520-

Arg603, Cys520-Glu607, Cys520-Val611, Cys520-Arg615, Cys520-Ala618, Lys577-Arg603, Lys577-Glu607, Lys577-Val611, Lys577-Arg615, Lys577-Ala618, Ser574-Arg603, Ser574-Glu607, Ser574-Val611, Ser574-Arg615, Ser574-Ala618, Val560-Arg603, Val560-Glu607, Val560-Val611, Val560-Arg615, Val560-Ala618, Cys544-Arg603, Cys544-Glu607, Cys544-Val611, Cys544-Arg615, and Cys544-Ala618.

38. (Amended) The ligand of claim 32, wherein the ligand binds to an epitope selected from the group consisting of QDPRLF (SEQ ID NO:10), LDPRLF (SEQ ID NO:11), KAIQDPRLF (SEQ ID NO:12), LDPRLFADEREI (SEQ ID NO:13), DENKANLDPRLF (SEQ ID NO:14), RLFADEREI (SEQ ID NO:15), and LDPRLFAD (SEQ ID NO:16).

49. (Amended) A method of claim 44, wherein the ligand binds to a peptide derived from human pIgR (SEQ ID NO: [2]1), selected from the group consisting of: Lys487-Arg603, Lys487-Glu607, Lys487-Val611, Lys487-Arg615, Lys487-Ala618, Cys520-Arg603, Cys520-Glu607, Cys520-Val611, Cys520-Arg615, Cys520-Ala618, Lys577-Arg603, Lys577-Glu607, Lys577-Val611, Lys577-Arg615, Lys577-Ala618, Ser574-Arg603, Ser574-Glu607, Ser574-Val611, Ser574-Arg615, Ser574-Ala618, Val560-Arg603, Val560-Glu607, Val560-Val611, Val560-Arg615, Val560-Ala618, Cys544-Arg603, Cys544-Glu607, Cys544-Val611, Cys544-Arg615, and Cys544-Ala618.

50. (Amended) The method of claim 44, wherein the ligand binds to an epitope of pIgR selected from the group consisting of QDPRLF (SEQ ID NO:10), LDPRLF (SEQ ID NO:11), KAIQDPRLF (SEQ ID NO:12), LDPRLFADEREI (SEQ ID NO:13), DENKANLDPRLF (SEQ ID NO:14), RLFADEREI (SEQ ID NO:15), and LDPRLFAD (SEQ ID NO:16).

71. (Amended) A method of claim 67, wherein the ligand selectively binds to a peptide derived from human pIgR (SEQ ID NO: [2]1), which peptide is selected from the group consisting of: Lys487-Arg603, Lys487-Glu607, Lys487-Val611,

Lys487-Arg615, Lys487-Ala618, Cys520-Arg603, Cys520-Glu607, Cys520-Val611, Cys520-Arg615, Cys520-Ala618, Lys577-Arg603, Lys577-Glu607, Lys577-Val611, Lys577-Arg615, Lys577-Ala618, Ser574-Arg603, Ser574-Glu607, Ser574-Val611, Ser574-Arg615, Ser574-Ala618, Val560-Arg603, Val560-Glu607, Val560-Val611, Val560-Arg615, Val560-Ala618, Cys544-Arg603, Cys544-Glu607, Cys544-Val611, Cys544-Arg615, and Cys544-Ala618.

72. (Amended) The method of claim 67, wherein the ligand binds to an epitope selected from the group consisting of QDPRLF (SEQ ID NO:10), LDPRLF (SEQ ID NO:11), KAIQDPRLF (SEQ ID NO:12), LDPRLFADEREI (SEQ ID NO:13), DENKANLDPRLF (SEQ ID NO:14), RLFADEREI (SEQ ID NO:15), and LDPRLFAD (SEQ ID NO:16).

85. (Amended) A method of claim 80, wherein the ligand binds to a peptide derived from human pIgR (SEQ ID NO: [2]1), selected from the group consisting of: Lys487-Arg603, Lys487-Glu607, Lys487-Val611, Lys487-Arg615, Lys487-Ala618, Cys520-Arg603, Cys520-Glu607, Cys520-Val611, Cys520-Arg615, Cys520-Ala618, Lys577-Arg603, Lys577-Glu607, Lys577-Val611, Lys577-Arg615, Lys577-Ala618, Ser574-Arg603, Ser574-Glu607, Ser574-Val611, Ser574-Arg615, Ser574-Ala618, Val560-Arg603, Val560-Glu607, Val560-Val611, Val560-Arg615, Val560-Ala618, Cys544-Arg603, Cys544-Glu607, Cys544-Val611, Cys544-Arg615, and Cys544-Ala618.

86. (Amended) The method of claim 80, wherein the ligand binds to an epitope of pIgR selected from the group consisting of QDPRLF (SEQ ID NO:10), LDPRLF (SEQ ID NO:11), KAIQDPRLF (SEQ ID NO:12), LDPRLFADEREI (SEQ ID NO:13), DENKANLDPRLF (SEQ ID NO:14), RLFADEREI (SEQ ID NO:15), and LDPRLFAD (SEQ ID NO:16).